COVID-19 STRATEGIC COMMENTARY

GATTACA SOLUTION NEEDED FOR COVID-19
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By Professor Frank Gannon

I do not watch many science fiction films; the reality is challenging enough. However, I recall the film Gattaca which I enjoyed almost 20 years ago. In it, the hero wanted to be an astronaut. He had a genetic defect that made him ineligible. He had to place his finger on a device to gain entry to the launch facility. The device instantly sequenced his DNA. He faked the material that was sampled and got to go to outer space. Today, we need a Gattaca-type device to define our COVID-19 status instantly before we go to work, fly, attend a sports event or live normally. It could be standard in our future; as ordinary as showing our ID or having a PIN for our credit card. Will it happen? I expect that the technology will be available for use quite soon as great progress being made, and there is a major engagement by companies worldwide to provide such a pregnancy-type test solution. It might be better accepted than the alternative of exclusion, and it could become part of the new normality. There are two categories of tests that are relevant; the first is to detect the genetic material of the virus. The second is to detect the immune response after infection. Published literature points to some promising outcomes for the two different diagnostic tests. But we are not there yet.

Genetic material testing

To deal with the detection of the genetic material first. We are learning that the virus is shed from an infected person a few days before they show any symptoms. Indeed, some people remain asymptotic. It follows that any *virus-free* pass card has to be based on a test performed on the day that it is used. The *gold standard* currently is a polymerase chain reaction (PCR) based method. The disadvantage is that it requires a few hours for a result, and it is best suited to handle a large number of samples simultaneously. Daily use in different countries suggests that the time to get a response is often more than a day from the time of sampling. That would not work at an airport, for example. Other nucleic acid amplification methods are showing promise for a more instant result. Some, such as LAMP (Loop mediated Isothermal Amplification), are performed at room temperature, and you can get the results in 30 minutes. And some, such as the Abbott ID Now, claim to have reduced the time to result to five minutes. One recent publication (1) listed 25 FDA-approved Nucleic Acid Amplification tests for use in certified laboratories as part of emergency fast-tracking procedures. There are many more in the pipeline. I have heard of two in Ireland that have the EU CE certification. So, let's presume that the number of busy labs at present is in the hundreds. In addition, there were three that were defined in the reference as a point of care test; the Abbott device, one from Cepheid and one from Mesa, which claims to have results in 30 minutes.

It is important to announce that you are active in the market, it is another matter to have a product that meets needs and matches the accepted gold standard. Some publications are emerging where some comparisons have been made. Some of these are referenced below (2-6, *note that where appropriate I include a brief excerpt from the publications listed below*). Reading these papers, there seem to be positive messages regarding the Cepheid process (and no conflicts of interest recorded by the authors). It took 45 minutes and seems to match the standard PCR laboratory test. There were some questions related to the Abbott process. As one report said; what is gained in time to result

(reported as 17 minutes), is lost in accuracy. I would read these analyses as a positive indication that an accurate rapid on-site test is going to be delivered from the commercial sector. It would bring a big financial benefit to the winner(s). Some publications (e.g. 7,8) show that the companies and researchers are working on changes to the reagents and sample preparation procedures. All will move to a point of care assay with minimal equipment (e.g. in a doctor's office or the airport) in the near future. It may require attendance at the airport, for instance, a little earlier than today, but that is within the norms that we are accustomed to. Indeed, the data point to an opportunity for an entrepreneur to establish a COVID-19 testing booth at the airport, and for the airlines to require a scan of the result before issuing a traveler with a flight boarding pass.

Immune response testing

The second approach is to show an immune response to a prior infection by COVID-19. As it takes approximately seven days for this titre to be detectable, it follows that the serum-based test (positive or negative) is not appropriate to decide if somebody is not a source infection. Negative could mean that it is too early to say rather than no virus is present. A positive result is currently viewed as likely to mean that the individual is post-infection and is protected, individually. At present, we do not know if that protection will ward off a second infection (although that seems probable) or how long that protected period will last. The message re T-Cell responses are not yet clear cut but will come in time. There have been hundreds of immunoassays proposed and launched to detect the human response or viral proteins. The targets are numerous and include IgA, IgM and IgG and combinations of these. The target proteins are also diverse. The studies that have reported so far may not be compelling (e.g. 11, 12) but only the earliest analysis have been published to date. More and better will come, but some patience is needed. The airport in Dubai rushed to introduce one such (IgM/IgG) immunoassay in April and then banned the test a month later when it was shown that the test was only 30 per cent accurate. Useless, in other words. So, any test that comes will have to show very solid data before it is accepted as giving reliable information.

Novel approaches

There is also the possibility of novel approaches that do not involve nucleic acid amplification or immunoassays. There are new diagnostics that depend on different biosensors, and we anticipate more progress there (13-15). Many groups are now skilled in rapid tests based on microfluidics, and they may also have a role to play.

The simplicity of a pregnancy test, where the time to a clear +/- response is minutes, shows what can be achieved. We are not yet at the stage of such a product, but there is optimism that it is an achievable goal. There are many detailed aspects of the diagnostic procedure to optimise (16). These include the source of the material (oral, nasal or blood from a finger prick or a larger amount), the time at which the sample is taken in the cycle of the disease and how the material is treated (either for nucleic acid or immune based assays). The crucial question is that of the specificity and the sensitivity of the assay in comparison with the gold standard and the accepted cut-off point for a negative answer. Much is at stake, and the global effort to provide a "pregnancy test" for COVID-19 suggests that it will be delivered, that is that a Gattaca device will be developed.

(1) Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus-2: A Narrative Review.
Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, Dittrich S, Yansouni CP. Cheng MP, et al. Ann Intern Med. 2020 Apr 13:M20-1301. doi: 10.7326/M20-1301. Online ahead of print. Ann Intern Med. 2020. PMID: 32282894

(2) Multi-center evaluation of cepheid xpert® xpress **SARS**-**CoV**-**2** point-of-care test during the **SARS**-**CoV**-**2** pandemic.
Wolters F, van de Bovenkamp J, van den Bosch B, van den Brink S, Broeders M, Chung NH, Favié B, Goderski G, Kuijpers J, Overdevest I, Rahamat-Langedoen J, Wijsman L, Melchers WJ, Meijer A.Wolters F, et al. J Clin Virol. 2020 May 11;128:104426. doi: 10.1016/j.jcv.2020.104426. Online ahead of print.J Clin Virol. 2020. PMID: 32417674
…(Cepheid)Xpert Xpress SARS-CoV-2 point of care test showed equal performance compared to routine in-house testing with a limit of detection (LOD) of 8.26 copies/mL. Other seasonal respiratory viruses were not detected. In clinical samples Xpert Xpress SARS-CoV-2 reaches an agreement of 100 % compared to all in-house RT-PCRs CONCLUSION: Cepheids GeneXpert Xpert Xpress SARS-CoV-2 is a valuable addition for laboratories in situations where rapid and accurate diagnostics are of the essence.

(3) In Vitro Diagnostic Assays for **COVID**-**19**: Recent Advances and Emerging Trends.
Vashist SK.Vashist SK. Diagnostics (Basel). 2020 Apr 5;10(4):202. doi: 10.3390/diagnostics10040202.Diagnostics (Basel). 2020. PMID: 32260471
…The main IVD assays used for COVID-19 employ real-time reverse transcriptase polymerase chain reaction (RT-PCR) that takes a few hours. But the assay duration has been shortened to 45 min by Cepheid. Of interest is the point-of-care (POC) molecular assay by Abbott that decreased the assay duration to just 5 min.

(4) Multicenter Evaluation of the Cepheid Xpert Xpress SARS-CoV-2 Test.

Loeffelholz MJ, Alland D, Butler-Wu SM, Pandey U, Perno CF, Nava A, Carroll KC, Mostafa H, Davies E, McEwan A, Rakeman JL, Fowler RC, Pawlotsky JM, Fourati S, Banik S, Banada PP, Swaminathan S, Chakravorty S, Kwiatkowski RW, Chu VC, Kop J, Gaur R, Sin MLY, Nguyen D, Singh S, Zhang N, Persing DH.Loeffelholz MJ, et al. J Clin Microbiol. 2020 May 4:JCM.00926-20. doi: 10.1128/JCM.00926-20. Online ahead of print. J Clin Microbiol. 2020. PMID: 32366669
…Xpert® Xpress SARS-CoV-2 (Xpert) test, a rapid, automated molecular test for SARS-CoV-2.
…The (Cepheid) Xpert test provided sensitive and accurate detection of SARS-CoV-2 in a variety of upper and lower respiratory tract specimens. The high sensitivity and fast time to results of approximately 45 minutes may impact patient management.

(5) Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the Rapid Detection of SARS-CoV-2.

Smithgall MC, Scherberkova I, Whittier S, Green DA.Smithgall MC, et al. J Clin Virol. 2020 May 13;128: 104428. doi: 10.1016/j.jcv.2020.104428. Online ahead of print.J Clin Virol. 2020. PMID: 32405252

…While (Cepheid) Xpert showed high agreement with cobas across a wide range of viral concentrations, this study highlights an important limitation of (Abbot) ID Now for specimens collected in viral or universal transport media with low viral concentrations. Further studies are needed to evaluate the performance of ID Now for direct swabs.

(6) Clinical Evaluation of Three Sample-To-Answer Platforms for the Detection of SARS-CoV-2.

Zhen W, Smith E, Manji R, Schron D, Berry GJ. Zhen W, et al. J Clin Microbiol. 2020 Apr 24: JCM.00783-20. doi: 10.1128/JCM.00783-20. Online ahead of print. J Clin Microbiol. 2020. PMID: 32332061

"…evaluate three sample-to-answer molecular diagnostic platforms (Cepheid Xpert® Xpress SARS-CoV-2 [Xpert Xpress], Abbott ID NOW™ COVID-19 [ID NOW], GenMark ePlex® SARS-CoV-2 Test [ePlex])

…The Xpert Xpress also had highest positive percent agreement (PPA) when compared to our reference standard (98.3%) followed by the ePlex (91.4%) and ID now (87.7%).

… All three assays showed 100% negative percent agreement (NPA). In the workflow analysis, the ID NOW produced the most rapid time to result per specimen (~17 minutes) as compared to the Xpert Xpress (~46 minutes) and the ePlex (~1.5 hours), but what the ID NOW gained in rapid results, it lost in analytical and clinical performance."

(7) **Rapid** detection of **SARS**-**CoV**-**2** by low volume real-time single tube reverse transcription recombinase polymerase amplification using an exo probe with an internally linked quencher (exo-IQ).
Behrmann O, Bachmann I, Spiegel M, Schramm M, El Wahed AA, Dobler G, Dame G, Hufert FT. Behrmann O, et al. Clin Chem. 2020 May 8: hvaa116. doi: 10.1093/clinchem/hvaa116. Online ahead of print. Clin Chem. 2020. PMID: 32384153

With a run time of 15 to 20 minutes and first results being available in under 7 minutes for high RNA concentrations, the reported assay constitutes one of the fastest nucleic acid based detection methods for SARS-CoV-2 to date and may provide a simple to use alternative to RT-qPCR for first-line screening at the point of need

(8) **SARS**-**CoV**-**2** detection by direct rRT-PCR without RNA extraction.
Merindol N, Pépin G, Marchand C, Rheault M, Peterson C, Poirier A, Houle C, Germain H, Danylo A. Merindol N, et al. J Clin Virol. 2020 May 7;128: 104423. doi: 10.1016/j.jcv.2020.104423. Online ahead of print. J Clin Virol. 2020. PMID: 32416598

"…In this study, we compared direct rRT-PCR method (without RNA extraction) using SeeGene AllplexTM 2019-nCoV rRT-PCR with the RealStar® SARS-CoV-2 rRT-PCR kit (Altona Diagnostics). We show that SeeGene and Altona's assays provide similar efficiency"

(9). Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Viro*l2020. *[*Epub ahead of print*]. .* doi:10.1002/jmv.2572 Li/Z.Yi.Y. Luo, X. et al

(10). SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv 2020.03.18.20038059. [Preprint.] 2020. doi: https://doi.org/10.1101/2020.03.18.200380597 pmid:32104917 Okba NMA, Müller MA, Li W, et al.

(11) Evaluation of commercial and automated **SARS**-**CoV**-**2** IgG and IgA ELISAs using **coronavirus** disease (**COVID**-**19**) patient samples.
Jääskeläinen AJ, Kekäläinen E, Kallio-Kokko H, Mannonen L, Kortela E, Vapalahti O, Kurkela S, Lappalainen M.Jääskeläinen AJ, et al. Euro Surveill. 2020 May;25(18):2000603. doi: 10.2807/1560-7917.ES.2020.25.18.2000603.Euro Surveill. 2020. PMID: 32400364
…We evaluated SARS-CoV-2 IgG and IgA ELISAs ……). Overall specificities were 91.9% and 73.0% for IgG and IgA ELISAs, respectively. Of 39 coronavirus disease patients, 13 were IgG and IgA positive and 11 IgA alone at sampling. IgGs and IgAs were respectively detected at a median of 12 and 11 days after symptom onset."

(12) Antibody Tests in Detecting SARS-CoV-2 Infection: A Meta-Analysis.
Kontou PI, Braliou GG, Dimou NL, Nikolopoulos G, Bagos PG.Kontou PI, et al. Diagnostics (Basel). 2020 May 19;10(5): E319. doi: 10.3390/diagnostics10050319.Diagnostics (Basel). 2020. PMID: 32438677
"…We identified 38 studies containing data from 7848 individuals. Tests using the S antigen are more sensitive than N antigen-based tests. IgG tests perform better compared to IgM ones and show better sensitivity when the samples were taken longer after the onset of symptoms. Moreover, a combined IgG/IgM test seems to be a better choice in terms of sensitivity than measuring either antibody alone. All methods yield high specificity with some of them (ELISA and LFIA) reaching levels around 99%. ELISA- and CLIA-based methods perform better in terms of sensitivity (90%-94%) followed by LFIA and FIA with sensitivities ranging from 80% to 89%. ELISA tests could be a safer choice at this stage of the pandemic."

(13) Current and Future Point-of-Care Tests for Emerging and New Respiratory Viruses and Future Perspectives.
Nelson PP, Rath BA, Fragkou PC, Antalis E, Tsiodras S, Skevaki C. Nelson PP, et al. Front Cell Infect Microbiol. 2020 Apr 29; 10:181. doi: 10.3389/fcimb.2020.00181. eCollection 2020.Front Cell Infect Microbiol. 2020. PMID: 32411619

"…Especially biosensors have the potential for a wider spectrum of applications. They also do not encounter the major limitation of NAATs as POCTs: the extraction of nucleic acids (Ali et al., 2017). For these tests, even less obvious complications, like the stability of the plastic materials against required chemicals, have to be overcome for future highly specific nucleic acid-based POCTs.v"

(14) Navigating the Pandemic Response Life Cycle: Molecular Diagnostics and **Immunoassays** in the Context of **COVID-19** Management.
Zhang J, Gharizadeh B, Lu D, Yue J, Yu M, Liu Y, Zhou M. Zhang J, et al. IEEE Rev Biomed Eng. 2020 Apr 29. doi: 10.1109/RBME.2020.2991444. Online ahead of print. IEEE Rev Biomed Eng. 2020. PMID: 32356761

(15)Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus-2: A Narrative Review. Trends and innovations in biosensors for **COVID-19** mass testing.
Santiago I. Santiago I. Chembiochem. 2020 May 4. doi: 10.1002/cbic.202000250. Online ahead of print. Chembiochem. 2020. PMID: 32367615
"….The present work surveys the landscape of available and emerging biosensor technologies for COVID-19 testing"

(16) **Covid-19**: testing times.
Beeching NJ, Fletcher TE, Beadsworth MBJ, Beeching NJ, et al. BMJ. 2020 Apr 8;369:m1403. doi: 10.1136/bmj.m1403.BMJ. 2020. PMID: 32269032